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Serum Dehydroepiandrosterone and DHEA-sulfate in Patients With Adult T-Cell Leukemia and Human T-Lymphotropic Virus Type I Carriers

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The serum levels of dehydroepiandrosterone (DHEA) and DHEA-sulfate (DHEA-S) were determined by radioimmunoassay in 38 patients with adult T-cell leukemia (ATL). Levels of serum DHEA and DHEA-S were also measured in 60 human T-lymphotropic virus type I (HTLV-I) carriers, and did not differ from those in 60 healthy control subjects. Serum levels in patients with ATL were lower than those in the age- and sex-matched healthy controls and in HTLV-I carriers with statistical significance. Serum DHEA and DHEA-S in male patients with acute and lymphoma-type ATL were 1.06 ± 0.77 ng/ml and 245.8 ± 192.9 ng/ml, respectively. Levels in male patients with chronic and smoldering-type ATL were 1.69 ± 0.68 ng/ml and 477.6 ± 251.5 ng/ml, respectively. Serum levels of DHEA and DHEA-S in patients with acute and lymphoma-type ATL were significantly lower than those in patients with chronic and smoldering-type ATL ($P < 0.05$).

These data suggest that a decrease in serum levels of DHEA and DHEA-S may be associated with patients who have some clinical subtypes of ATL. Moreover, androgens may have a therapeutic role in patients with ATL, as administered in patients with hairy-cell leukemia. Because there is at present no curative chemotherapy for ATL, a trial combination of androgens and standard chemotherapy may be a reasonable therapeutic option in such patients. © 1996 Wiley-Liss, Inc.

Key words: DHEA, DHEA-S, ATL, HTLV-I carrier

INTRODUCTION

Dehydroepiandrosterone (DHEA) and DHEA-sulfate (DHEA-S) are secreted by the adrenal cortex in abundant quantities, but their definitive biological function has not been described, except in endocrinology. DHEA has a wide range of effects in a variety of diseases, and exhibits immunoregulatory [1–3], anticancer, and antistress activity [4]. DHEA is also involved in preventing atherosclerosis [5,6] and death from cardiovascular diseases in men over age 50 [7]. Serum levels of DHEA and DHEA-S are reportedly decreased in patients with HIV infection [8], Alzheimer's disease and multiinfarct dementia [9], breast cancer [10], hairy-cell leukemia [11], and prostatic cancer [4].

Adult T-cell leukemia (ATL) is a peripheral T-cell neoplasm that is characterized by the presence of immunodeficiency and the development of opportunistic infections [12]. We know of no studies on the production of adrenal androgens in patients with ATL, although these steroids profoundly influence the immune response [1–3] as well as carcinogenesis [13,14]. It has been reported that DHEA and DHEA-S in patients with hairy-cell leukemia (HCL) are decreased, and this decrease in adrenal androgens production may contribute to the immunological impairment in HCL [11]. In this study, we determined the serum levels of DHEA and DHEA-S in patients with ATL and in human T-lymphotropic virus type I (HTLV-I) carriers, in order to determine whether ATL patients also have decreased levels of serum DHEA and DHEA-S, and to

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see if serum levels of DHEA and DHEA-S were different between clinical subtypes [12] of ATL patients.

MATERIALS AND METHODS

Thirty-eight Japanese patients with ATL were studied. These were 28 men and 10 women, age 42–65 years, median age 61 years. They had received no previous chemotherapy or corticosteroid treatment at time of serum sampling. Serum samples were collected with informed consent. Patients with ATL included four clinical subtypes [12]. Twenty-two patients (14 men and 8 women) had acute-type ATL. Six patients (4 men and 2 women) had lymphoma-type ATL. Five male patients had chronic, and another 5 men smoldering-type, ATL. Eleven patients had performance status (PS) [15] 0, 12 patients had PS 1, 13 patients had PS 2, and only 2 patients had PS 3. There was no patients with PS 4. Thirty male and 30 female HTLV-I carriers (age 41–65 years), and 30 male and 30 female healthy subjects (age 41–65 years), were also investigated as control subjects. Serum samples from HTLV-I carriers and healthy subjects were randomly collected from donated blood from volunteers through the courtesy of the Kagoshima Red Cross Blood Center. All serum samples were stored at −80°C until assayed.

Serum DHEA and DHEA-S levels were determined by radioimmunoassay (RIA). Specific antibody used in the RIA for DHEA was produced against 11α-succinoyloxy-DHEA-bovine serum albumin (BSA). Serum DHEA-S levels were assayed with the DHEA-S RIA kit (Coat-A-Count® DHEA-SO_4, Diagnostic Product Corporation, Los Angeles, CA). It is possible for this kit to make measurements in the range of 6–10,000 ng/ml. Independent measurements of DHEA and DHEA-S were performed with duplicate aliquots of serum samples for confirmation of the values. Data are shown as the mean ± standard deviation of the mean value of each sample. The values of serum DHEA and DHEA-S in patients with ATL were compared with those of appropriate age- and sex-matched control groups. Statistical analysis used Student's t-test. $P < 0.05$ was regarded as statistically significant.

RESULTS

Healthy Subjects and HTLV-I Carriers

Serum levels of DHEA and DHEA-S in healthy subjects and HTLV-I carriers are shown in Table I. There was no statistically significant difference between serum levels of DHEA and DHEA-S in HTLV-I carriers and in healthy subjects.

Patients With ATL

Serum levels of DHEA and DHEA-S in patients with ATL are also shown in Table I according to age and sex. Except for women in their 40's and 50's, serum DHEA and DHEA-S levels in patients with ATL were lower than those of age- and sex-matched healthy subjects and HTLV-I carriers with statistical significance.

Clinical Subtype of ATL

Serum levels of DHEA and DHEA-S in male patients with acute and lymphoma-type ATL were significantly ($P < 0.05$) lower than in male patients with chronic and smoldering-type ATL (Fig. 1).

DISCUSSION

ATL is a fatal neoplasm of CD4(+) mature peripheral lymphocytes that is caused by HTLV-I. ATL probably results from multistep leukemogenesis [16], whose steps are unclear except for the initial HTLV-I infection.

DHEA has recently been found effective in preventing cardiovascular diseases [7] and carcinogenesis [13,14]. It has also been reported that DHEA and DHEA-S levels in patients with HCL are decreased [11].

Although we found significantly lower DHEA and DHEA-S levels in patients with ATL, levels in HTLV-I carriers were not lower than in age- and sex-matched healthy subjects. Therefore, it is thought that decreased levels of DHEA and DHEA-S in patients with ATL are not due to infection with HTLV-I. DHEA and DHEA-S are effective in preventing spontaneous and chemically induced experimental carcinogenesis in animal models [13,14], and bladder cancer in man [17]. DHEA protects against the virus-induced transformation of human lymphocytes [18]. DHEA inhibits lymphopoiesis by preventing the differentiation and/or proliferation of progenitor cells [1] and represents a potent enhancer of IL-2 production by activated T-cells [2]. Considering these effects of DHEA and DHEA-S, the decrease in levels of DHEA and DHEA-S may be one step in the leukemogenesis of CD4(+) lymphocytes by HTLV-I.

According to the clinical subtypes of ATL, serum levels of DHEA and DHEA-S in acute and lymphoma types were significantly lower than in chronic and smoldering types. Although it is not clear whether these differences between clinical subtypes were caused by a difference in general conditions or in disease activities, low levels of DHEA and DHEA-S may be one explanation for the difference in clinical subtypes.

Because DHEA upregulates the host immune response [19] and potentiates in vitro lymphocyte activation [3], a decrease in adrenal androgen production may contribute to the immunological impairment in ATL. Except for 2 patients with PS 3, the remaining 36 patients had moderately good general conditions. However, their serum levels of DHEA and DHEA-S were already lower than those of healthy controls at earliest diagnosis. In HCL, in which serum levels of DHEA and DHEA-S are low [11], treatment with androgens is partially effective [20,21]. Therefore, as there is no curative chemotherapy for ATL [22],

TABLE I. Serum Levels of DHEA and DHEA-S in Patients With ATL and Control Subjects by Age and Sex†

Age (years)	Condition	Sex	No. of patients	DHEA (ng/ml)	DHEA-S (ng/ml)
40–49	ATL	Male	7	1.34 ± 0.59***	421.4 ± 255.4***
		Female	1	1.030	199.0
	HTLV-I carriers	Male	10	3.16 ± 1.24	1311.7 ± 437.8
		Female	10	3.50 ± 1.09	1042.7 ± 517.4
	Healthy subjects	Male	10	4.39 ± 1.69	1372.7 ± 469.6
		Female	10	3.84 ± 1.66	703.6 ± 396.2
50–59	ATL	Male	7	1.33 ± 0.83**	307.1 ± 243.3**
		Female	2	1.70 ± 1.44 (n.s.)	326.5 ± 163.3 (n.s.)
	HTLV-I carriers	Male	10	2.92 ± 1.09	1467.2 ± 945.8
		Female	10	1.95 ± 0.70	438.1 ± 368.8
	Healthy subjects	Male	10	3.01 ± 1.21	1205.1 ± 583.3
		Female	10	3.17 ± 1.64	897.3 ± 563.7
60–69	ATL	Male	14	1.23 ± 0.90***	292.9 ± 235.2***
		Female	7	1.22 ± 0.77*	261.7 ± 244.8*
	HTLV-I carriers	Male	10	2.62 ± 1.05	882.8 ± 333.4
		Female	10	2.45 ± 1.13	362.7 ± 240.0
	Healthy subjects	Male	10	3.18 ± 1.02	1292.5 ± 547.2
		Female	10	2.69 ± 1.27	676.8 ± 429.4

†n.s., not significant.
*$P < 0.05$.
**$P < 0.01$.
***$P < 0.001$.

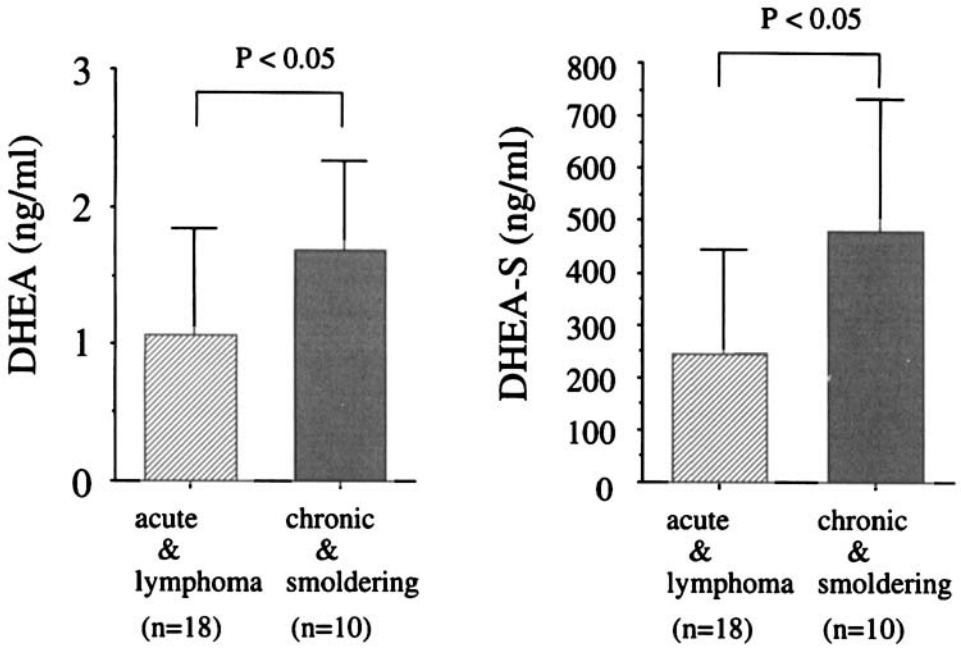

Fig. 1. Serum levels of DHEA and DHEA-S in male patients, according to clinical subtypes of ATL. Error bar indicates standard deviation.

a trial combination of androgens and standard chemotherapy may be a reasonable therapeutic option in patients with ATL.

CONCLUSIONS

We measured serum levels of DHEA and DHEA-S by RIA in 38 patients with ATL, 60 HTLV-I carriers, and 60 healthy control subjects. Serum levels in patients with ATL were lower than in age- and sex-matched healthy controls and in HTLV-I carriers with statistical significance. Serum levels of DHEA and DHEA-S in patients with acute and lymphoma-type ATL were significantly lower than in patients with chronic and smoldering-type ATL ($P < 0.05$). These data suggest that a decrease in serum levels of DHEA and DHEA-S may be associated

with patients who have some clinical subtypes of ATL. Moreover, treatments with combination of androgens and standard chemotherapy may have some therapeutic role in patients with ATL, as administered for HCL.

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